CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 2-2011: A 30-Year-Old Woman with Shock after Treatment of a Furuncle

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PRESENTATION OF CASE

Dr. Ari Brettman (Medicine): A 30-year-old woman was transferred to this hospital because of hypotension and respiratory failure.

The patient had been well until 4 days before admission, when she slipped and fell in her home, after which she reported severe posterior thoracic pain that radiated to the anterior chest and lower back and did not respond to acetaminophen. Two days later, she went to an urgent care clinic affiliated with this hospital. She rated the pain at 10 on a scale of 0 to 10, with 10 indicating the most severe pain; she reported that the pain increased with movement and breathing. She reported mildly decreased appetite, without nausea, vomiting, or weakness. On examination, she appeared comfortable; the temperature was 36.6°C, the blood pressure 102/59 mm Hg, the pulse 100 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. The thoracic paraspinal muscles were tender, with spasm; the remainder of the examination was normal. Radiographs of the chest and thoracic spine were normal. Ketorolac tromethamine was administered intramuscularly. The patient went home, with instructions to return if the pain did not resolve. The next day, she went to another hospital because of persistent pain. Cyclobenzaprine and oxycodone with acetaminophen were prescribed, and she returned home. On the day of admission, at approximately 8:30 p.m., a friend found her at home, unresponsive and moaning. Emergency medical services personnel were called, and the patient was taken to the other hospital by ambulance. Naloxone was administered en route, with minimal response.

On arrival in the emergency department, the patient was agitated and aphasic and responded to painful stimuli. The rectal temperature was 39.6°C, the blood pressure 113/53 mm Hg, the pulse 156 beats per minute, the respiratory rate 46 breaths per minute, and the oxygen saturation 83% while she was breathing ambient air. The skin was gray, warm, and clammy, and there were small cutaneous vesicles on the forehead and abdomen. The neck was supple. The left pupil was 5 mm in diameter and the right pupil 4 mm, and both were minimally reactive. The breath sounds were decreased in intensity without adventitious sounds, the nail beds were cyanotic, and plantar reflexes were flexor. The remainder of the examination was normal. The administration of 15 liters of oxygen by means of a nonrebreather

mask was begun, and acetaminophen was administered rectally. Toxicologic screening of the plasma revealed the presence of salicylates, and analysis of the urine revealed opiates; other laboratory-test results are shown in Table 1. Three ampules of sodium bicarbonate were administered intravenously. A chest radiograph reportedly showed diffuse pulmonary infiltrates, and computed tomography (CT) of the head was reportedly normal. Oxygen saturation was 81% while she was receiving supplemental oxygen by means of a nonrebreather face mask. The trachea was intubated, and mechanical ventilation was begun. Intravenous vancomycin and midazolam were administered. The blood pressure decreased to 73/20 mm Hg; norepinephrine bitartrate, normal saline, and an additional two ampules of bicarbonate were infused; the blood pressure rose transiently to 145/90 mm Hg, then fell to 112/20 mm Hg. Approximately 2.5 hours after arrival, the patient was transferred to this hospital by ambulance, while piperacillin and tazobactam sodium were being infused. During transport, pulseless electrical activity developed; cardiopulmonary resuscitation was performed, and a pulse was restored.

One month earlier, the patient had been seen in an urgent care clinic affiliated with this hospital because of a red, hard, painful lump that had developed on her right lower leg 3 days earlier. On examination at that time, the temperature was normal. There was an abscess with local erythema (1.5 cm in diameter) on the right upper pretibial region; distal circulation and sensory and motor examinations were normal. The lesion was incised under sterile conditions with local anesthesia, and purulent bloody discharge was drained and cultured; a wick was inserted and a dry sterile dressing applied. A 10-day course of cephalexin (500 mg four times daily) and trimethoprim–sulfamethoxazole (double-strength twice daily) was prescribed. Two days later, cultures grew *Staphylococcus aureus* that was resistant to oxacillin, penicillin G, levofloxacin, and erythromycin and susceptible to clindamycin, vancomycin, tetracycline, and trimethoprim–sulfamethoxazole. The patient was notified by telephone; she had not begun the antibiotics and declined to return for reevaluation. She reportedly obtained the antibiotics that day and completed the 10-day course. She had been well otherwise. She lived alone and worked in an office. She reportedly did not smoke or use illicit drugs and had not traveled or had recent exposure to animals. She had no known allergies to medications.

On examination, she was unresponsive, with cool, mottled extremities. The blood pressure was 122/90 mm Hg, the pulse 141 beats per minute, the temperature 37.4°C, and the respiratory rate 30 breaths per minute, while she was on mechanical ventilation. The neck was supple. Coarse, loud rales were heard throughout both lungs on inspiration and expiration; there were no cardiac murmurs, and the abdomen was distended and firm without organomegaly. There was a diffuse papular and pustular rash on the face, neck, chest, and abdomen and a healing ulcer with eschar (1 cm in diameter) on the right lower leg, with no erythema, crepitus, or necrosis. The hands and feet were cool and cyanotic; there were no lesions on the palms or soles. Pelvic examination revealed a white, thick, foul-smelling vaginal discharge, with no intravaginal foreign body or intrauterine device. Toxicologic screening of plasma revealed the presence of cyclobenzaprine and oxycodone, and the urine was positive for benzodiazepines, tricyclic antidepressants, and acetaminophen; other laboratory-test results are shown in Table 1. An electrocardiogram revealed sinus rhythm at 142 beats per minute, with nonspecific ST-segment and T-wave abnormalities.

Within 15 minutes after arrival, the blood pressure decreased to 74/56 mm Hg. Central venous and radial arterial catheters were placed. Isotonic intravenous fluids and norepinephrine were infused to maintain a mean arterial pressure of 65 mm Hg. Trimethoprim–sulfamethoxazole, acyclovir, stress doses of glucocorticoids, bicarbonate, calcium gluconate, normal saline, fresh-frozen plasma, cryoprecipitate, and albumin were administered. CT of the brain, without the administration of contrast material, revealed multiple, diffuse, hyperdense foci in the frontal, parietal, temporal, and occipital lobes bilaterally, many at the junction of the gray and white matter and along the corpus callosum, locations that are consistent with intraparenchymal hemorrhage; there was also surrounding hypodensity, which was consistent with edema. CT of the chest, obtained without the administration of contrast material, revealed diffuse bilateral patchy areas of consolidation and ground-glass opacities in the lungs, with superimposed intralobular septal thickening, small focal cavitations in the right upper and left lower lobes, and small bilateral pleural effusions. CT of the abdomen

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Other Hospital, on Presentation	This Hospital	
			On Evaluation, in the Emergency Department	4 Hr after Presentation, in the Intensive Care Unit
Hematocrit (%)	36–46 (women)	38.7	31.3	29.8
Hemoglobin (g/dl)	12–16 (women)	12.9	10.6	9.9
White cells (per mm^3)	4500–11,000	2500	1500	1600
Differential count (%)				
Neutrophils	40–70	39 (ref 46–79)	14	0
Band forms	0–10	14 (ref 0–8)	3	0
Lymphocytes	22–44	34	72	88
Monocytes	4–11	5	0	0
Eosinophils	0–8	2	2	0
Basophils	0–3	0	0	0
Metamyelocytes	0	3 (ref 0)	9	1
Myelocytes		3 (ref 0)	0	0
Atypical or reactive lymphocytes	0	0	0	11
Platelets (per mm^3)	150,000–400,000	108,000	59,000	39,000
ABO blood type			Type O, Rh-positive, negative antibody screening	
D-Dimer (ng/ml)	<500		6895	6733
Fibrinogen (mg/dl)	150–400		418	246
Activated partial-thromboplastin time (sec)	22.1–34.0	39.5	51.4	96.2
Prothrombin time				
Seconds	10.3–13.2	17.0	23.0	28.1
International normalized ratio		1.7	2.3	2.9
Arterial blood gas				
Fraction of inspired oxygen		1.00	1.00	1.00
pH	7.35–7.45	6.98	7.21	6.88
Partial pressure of oxygen (mm Hg)	80–100	90.0	57	36
Partial pressure of carbon dioxide (mm Hg)	35–42	45.90	40	69
Bicarbonate (mmol/liter)	24–30		15	
Sodium (mmol/liter)	135–145	142	148	150
Potassium (mmol/liter)	3.4–4.8	5.1	4.1	5.8
Chloride (mmol/liter)	100–108	103	106	116
Carbon dioxide (mmol/liter)	23.0–31.9	11	14.2	11.5
Anion gap (mmol/liter)	3–15	28	28	23
Urea nitrogen (mg/dl)	8–25	55	51	46
Creatinine (mg/dl)	0.60–1.50	6.6	4.84	4.46
Glucose (mg/dl)	70–110	79	90	56
Total bilirubin (mg/dl)	0.0–1.0	1.0	0.8	0.8
Protein (g/dl)				
Total	6.0–8.3	5.2	3.8	2.8
Albumin	3.3–5.0	2.4	1.8	1.2
Globulin	2.6–4.1		2.0	1.6

Table 1. (Continued.)

Variable	Reference Range, Adults†	Other Hospital, on Presentation	This Hospital	
			On Evaluation, in the Emergency Department	4 Hr after Presentation, in the Intensive Care Unit
Phosphorus (mg/dl)	2.6–4.5		9.7	9.6
Magnesium (mg/dl)	1.7–2.4		2.4	2.2
Calcium (mg/dl)	8.5–10.5	7.0	5.0	4.4
Ionized calcium (mmol/liter)	1.14–1.30		0.88	0.76
Lactic acid (mmol/liter)	0.5–2.2		13.5	12.4
Alkaline phosphatase (U/liter)	30–100	51	38	49
Aspartate aminotransferase (U/liter)	9–32	2272	2907	2400
Alanine aminotransferase (U/liter)	7–30	837	1233	1016
Lactate dehydrogenase (U/liter)	110–210		2772	
Lipase (U/liter)	13–60		45	49
Amylase (U/liter)	3–100		222	229
Creatine kinase (U/liter)	40–150		18,975	18,840
Creatine kinase MB isoenzymes (ng/ml)	0.0–6.9		235.1	231.0
Troponin T (ng/ml)	0.0–0.09		0.58	0.89
NT-pro-BNP (pg/ml)	Age <50 yr: 0–450		52,753	57,208
Human chorionic gonadotropin	Negative	Negative	Negative	
Urinalysis				
pH	5.0–9.0	5.5	5.5	
Specific gravity	1.001–1.035	1.030	>1.030	
Appearance	Yellow, clear	Brown, turbid	Yellow, cloudy	
White cells	Negative	Negative	Negative	
Nitrites	Negative	Negative	Positive	
Urobilinogen	Negative	0.2 Ehrlich units/dl	Negative	
Albumin	Negative	100 mg/dl	2+	
Glucose	Negative	Negative	Negative	
Ketones	Negative	15 mg/dl	Trace	
Blood	Negative	3+	3+	
Bilirubin	Negative		Negative	
Sediment (per high-power field)				
Bacteria	None	10–50	Few	
Red cells	0–2	3–4	10–20	
White cells	0–2	5–10	50–100	
White-cell casts	None	Rare (per low-power field)		
Squamous epithelial cells	None	>10 (per low-power field)	Few	
Amorphous crystals	None		Present	

* NT-pro-BNP denotes N-terminal fragment of pro–brain (B-type) natriuretic peptide, and ref the reference range at the other hospital. To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the value for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

and pelvis revealed a small amount of perihepatic fluid, a mixture of fluid and soft-tissue attenuation in the portal region that was suggestive of mild lymphadenopathy, and a band of increased attenuation along the right lower pelvic sidewall that was suggestive of a hematoma. There was no free intraperitoneal air or abscess.

The patient was admitted to the intensive care unit. Ceftriaxone, clindamycin phosphate, meropenem, gentamicin, and doxycycline were administered. Hypoxemia, hypercarbia, acidosis, and hypotension worsened, despite maximal support with pressors; the pupils became fixed and dilated. In consultation with the family, resuscitative measures were stopped, and the patient died, less than 12 hours after arrival at this hospital.

A diagnostic test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Robert C. Moellering, Jr.: May we see the imaging studies?

Dr. Gerald F. Abbott: On the day of admission, CT of the brain (Fig. 1A) revealed minimal mucosal thickening in the ethmoid sinuses, and the mastoid air cells were clear; there was no evidence of acute sinusitis. Axial images through the brain showed multiple foci of hyperintensity in the bilateral frontal, temporal, parietal, and occipital lobes; many of the foci were located along the gray–white junction and the corpus callosum, findings that were consistent with intraparenchymal hemorrhage. There were also subtle surrounding areas of hypodensity, which were consistent with edema. Differential diagnostic considerations included septic emboli to the brain, with associated hemorrhage, and hemorrhagic metastases, such as those associated with melanoma, renal-cell carcinoma, thyroid carcinoma, and choriocarcinoma.

A chest radiograph obtained with a portable device (Fig. 1B) on the day of admission shows diffuse bilateral air-space and reticular abnormalities and bilateral pleural effusions. These changes are better seen on an unenhanced CT scan of the chest (Fig. 1C and 1D) that shows extensive bilateral areas of consolidation predominantly involving the dependent portions of both lungs, with patchy areas of ground-glass opacity and associated smooth thickening of interlobular septa. There were small areas of cavitation in both lungs.

An unenhanced CT scan of the abdomen and pelvis (Fig. 2A and 2B) showed a mixture of fluid and soft-tissue density in the region of the porta hepatis that was suggestive of ascites and mild lymph-node enlargement. There was fluid along the edge of the liver (Fig. 2A), and a band of soft-tissue density (Fig. 2B) adjacent to a right femoral catheter, features that were consistent with a hematoma. There was no evidence of abscess formation in the abdomen or pelvis, but the study was limited by the lack of intravenous contrast administration.

Dr. Moellering: One month after treatment and resolution of an abscess of the left leg caused by infection with community-acquired methicillin-resistant *Staph. aureus* (MRSA), this previously healthy 30-year-old woman was transferred to this hospital; she was critically ill with signs and symptoms that were consistent with overwhelming sepsis. Despite intensive antimicrobial and resuscitative therapy, she remained unresponsive and died.

SEPSIS SYNDROME

Potential causes of overwhelming sepsis in this patient include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Strep. pyogenes*, viridans streptococci (especially the *Strep. anginosus* group [formerly the *Strep. milleri* group]), enterococci, clostridium species, gram-negative bacilli (Enterobacteriaceae and nonfermenting species), candida or other fungi, or *Staph. aureus* (MRSA). *Strep. pneumoniae* can cause overwhelming sepsis, but except for serogroup 3, cavitary pneumonia due to this organism is distinctly unusual. Moreover, it appears that the pneumonia in this patient was a secondary complication of bacteremic spread. *N. meningitidis* can cause pneumonia and overwhelming sepsis, but the rash is not consistent with meningococcemia, and this organism would be unlikely to cause cavitary pneumonia. *Strep. pyogenes* can also cause overwhelming sepsis with pulmonary involvement, as well as early pleural effusions, such as those that were seen here. Although the presence of early cavitation makes *Strep. pyogenes* unlikely, it would be impossible to rule it out completely on the basis of the initial data. Viridans streptococci (especially the *Strep. anginosus* group) can cause multiple abscesses, but overwhelming sepsis would be unusual. Enterococci and clostridia rarely if ever infect the lung. There is no obvious source for

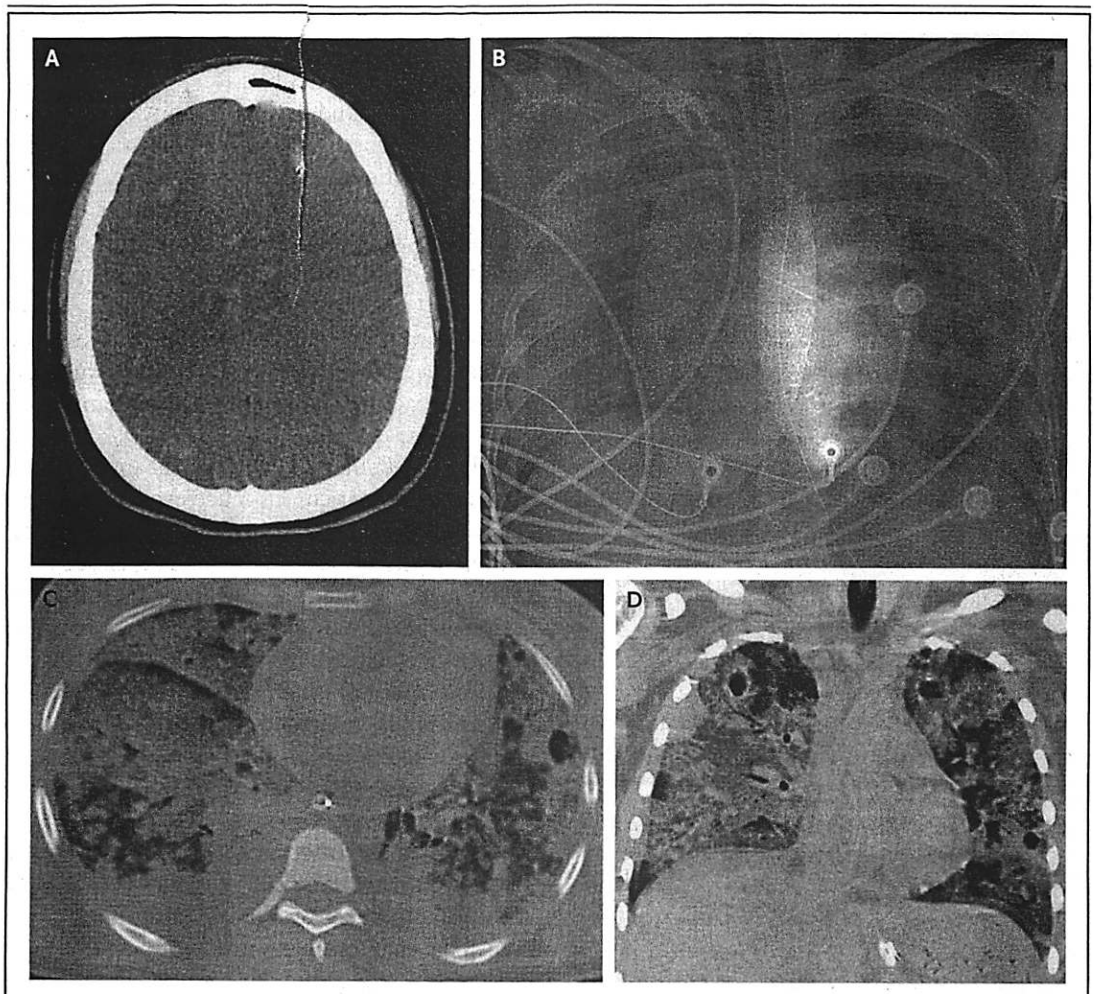

Figure 1. Imaging Studies of the Brain and Chest.
An unenhanced CT scan of the brain (Panel A) shows multiple foci of hyperintensity in both frontal and parietal lobes, distributed along the junction of the gray and white matter and also along the corpus callosum. Subtle areas of surrounding hypointensity are consistent with edema. A chest radiograph obtained with a portable device (Panel B) shows diffuse bilateral air-space and reticular opacities and bilateral pleural effusions. Axial (Panel C) and coronal (Panel D) images from an unenhanced chest CT show extensive bilateral areas of consolidation and patchy areas of ground-glass opacities, with associated smooth thickening of interlobular septa, and small areas of cavitation in both lungs.

gram-negative bacilli, such as a urinary tract infection or an intraabdominal or a pelvic source. Finally, candida also seems highly unlikely.

STAPH. AUREUS INFECTIONS

That leaves *Staph. aureus* as the most likely cause of this syndrome. Staphylococcal pneumonia is often associated with early cavitation. In this patient, I suspect that pneumonia is the result of bacteremic spread to the lung, but several other possibilities must be considered. The patient has multiple lesions in the brain, raising the possibility of either metastatic abscesses or septic emboli from acute left-sided bacterial endocarditis. Septic pulmonary emboli are commonly seen in right-sided endocarditis. The lesion that was noted along the right iliac vessels raises the possibility of a septic pelvic thrombophlebitis, in which case septic pulmonary emboli due to *Staph. aureus* could account for the pulmonary involvement as well. The skin lesions (described as crops of pustular or vesicular lesions over the forehead, trunk,

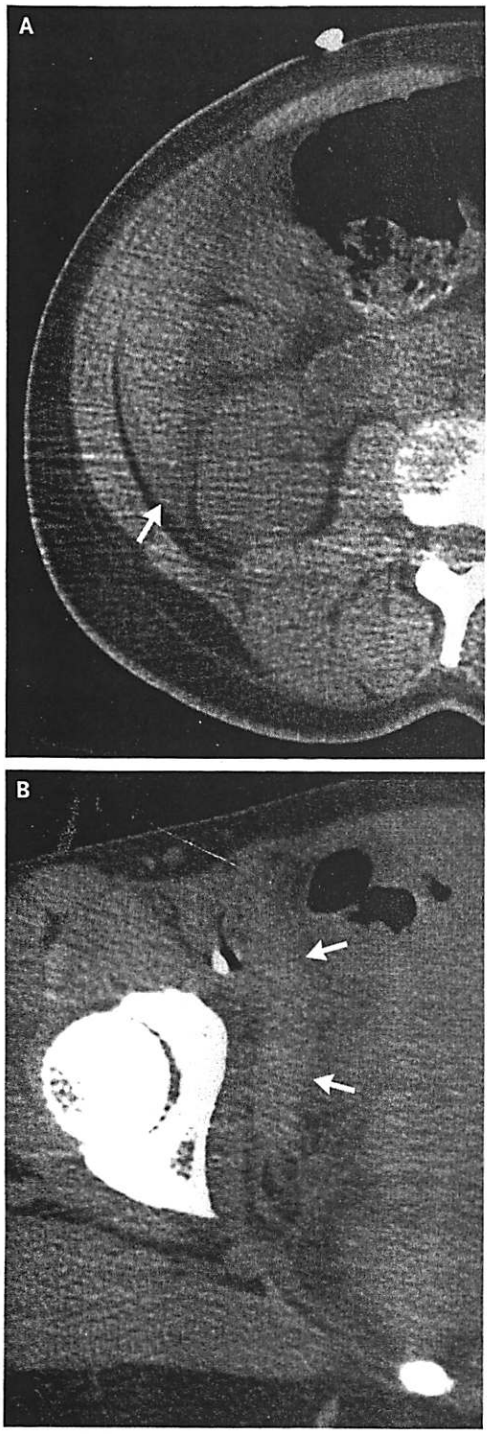

Figure 2. Imaging Studies of the Abdomen and Pelvis.
An unenhanced abdominal and pelvic CT scan shows perihepatic ascites (Panel A, arrow) and a band of hyperattenuating soft-tissue density (Panel B, arrows) adjacent to a right femoral catheter, features that are consistent with a hematoma.

and abdomen) are consistent with lesions that may be seen in staphylococcal bacteremia. Therefore, the clinical evidence strongly suggests cavitary pneumonia and overwhelming sepsis due to MRSA, with septic emboli or metastatic abscesses in various tissues, including the brain.

This case raises a number of questions, including the most important: Why should a previously healthy 30-year-old die precipitously from overwhelming staphylococcal disease? In order to begin to answer, it would help to review briefly the clinical diseases caused by *Staph. aureus* and the virulence factors that enable this organism to cause severe disease. *Staph. aureus* can cause as varied a set of clinical infections as any microorganism known. It can produce everything from chronic skin infections, such as botryomycosis, to overwhelming and rapidly fatal sepsis, as seen in this case. It can infect virtually all tissues of the body except the hair, teeth, and fingernails. The organism produces toxins that are associated with food poisoning, enterocolitis, toxic epidermal necrolysis, toxic shock syndrome, and necrotizing pneumonia.

STAPH. AUREUS VIRULENCE FACTORS

Virulence factors produced by *Staph. aureus* include cell-wall constituents that serve as adhesins to allow the organism to bind to and penetrate human cells, enzymes that facilitate tissue invasion, and polypeptide toxins that damage cell membranes and can serve as superantigens. Enterotoxins (including the toxic shock syndrome toxin 1 [TSST-1]) and exfoliatin exotoxins can activate T lymphocytes, leading to the liberation of cytokines that produce fever, hypotension, skin lesions, shock, multiorgan failure, and death. It is highly likely that such superantigens contributed to the picture of overwhelming sepsis that was seen in our patient. The production of virulence factors is controlled by several regulatory systems, including the accessory gene regulator (*agr*).[1]

COMMUNITY-ACQUIRED MRSA

This patient's MRSA infection was acquired in a community setting, unlike the majority of infections due to MRSA, which until recently were nosocomial, a result of spread in hospitals or nursing homes. Within the past decade, such community-acquired infections with MRSA have been increasingly reported. Community-acquired MRSA strains from many parts of the world share staphy-

lococcal cassette chromosome *mec* (SCC*mec*) type IV (unlike hospital-associated strains, in which types I, II, and III are seen), which contains the genes responsible for methicillin resistance. Most community-associated MRSA also contain the genes for the Panton–Valentine leukocidin (PVL) toxin. Other toxin genes are specific to strains from each geographic area. The community-associated strains are fully virulent and as capable of causing fatal infections as are hospital-acquired strains,[2] as I believe we saw in this case.

How did this patient acquire community-acquired MRSA? The first outbreaks in the United States were reported among rural Native American children in 1999.[2] Shortly thereafter, outbreaks occurred in men who have sex with men, prison inmates, and participants in contact sports. By 2005, in some cities, 63 to 76% of all the community-acquired strains of *Staph. aureus* were methicillin-resistant. Thus, virtually everyone in the United States is now at risk for the development of community-acquired MRSA infections. In addition to widespread dissemination of these organisms in the community, they have been introduced into hospitals, blurring the distinction between community-acquired MRSA and hospital-acquired MRSA.

As the epidemic of community-acquired MRSA infections has progressed, new syndromes have been described. The majority of patients have infections of the skin and soft tissues, as this patient initially had. Other more serious infections include necrotizing fasciitis; pyomyositis; septic thrombophlebitis of the extremities; a "pelvic syndrome" consisting of septic arthritis of the hips, pelvic osteomyelitis, pelvic abscesses, and septic pelvic-vein thrombophlebitis; Waterhouse–Friderichsen syndrome; and rapidly progressive necrotizing pneumonia.[3] It is likely that rapidly progressive necrotizing pneumonia occurred in this patient and proved fatal.

One particular clone (USA300) accounts for 90 to 95% of the outpatient isolates in the United States and, I predict, infected this patient. USA300 has a number of genetic characteristics that may give it a selective advantage over other clones.[4-6] However, although the mechanism by which it can cause serious infections in humans has been the subject of intensive studies, a definitive explanation has yet to be revealed. PVL per se is not associated with virulence in mouse models. The arginine catabolic mobile element found on SCC*mec* type IV, the alpha-toxin, and overexpression of phenol-soluble modulin peptides, which cause lysis of polymorphonuclear leukocytes, have all been shown to lead to increased virulence. Concomitant up-regulation of *PVL* expression may also contribute to virulence.[7,8] Unfortunately, none of these studies explain why strains of community-acquired MRSA containing identical genes cause mild disease in some patients and overwhelming infections in other patients, such as this one. The answer may lie in a combination of bacterial gene expression and host factors.[9,10] As is true for *Strep. pyogenes*, inhibitors of bacterial protein synthesis, such as clindamycin or linezolid, can decrease toxin production in cases of community-acquired MRSA and may have a therapeutic role in patients, such as this one, who have overwhelming sepsis.[7,8,11,12]

SUMMARY

I believe this patient died of sepsis due to infection with community-acquired MRSA. My questions to the microbiologists include the following. What was the infecting organism? Assuming it was *Staph. aureus*, were studies performed to determine whether the strain was USA300? Were studies of the organism performed to look for genes encoding TSST-1 or other enterotoxins or for other virulence factors?

Dr. Nancy Lee Harris (Pathology): May we have the medical students' diagnosis?

A Harvard Medical Student: In this case of fulminant sepsis in an otherwise apparently healthy patient, who had a constellation of clinical symptoms and radiographic findings including cavitary lung lesions, MRSA was highest on our list of likely diagnoses. In view of the susceptibility patterns of the organism cultured from the ulcer on her leg, we thought community-acquired MRSA with overwhelming sepsis was the most likely diagnosis.

Dr. Harris: Dr. Sievers, would you tell us the thinking of the care team at the time?

Dr. Amy Sievers (Infectious Diseases): There are a very limited number of organisms that can cause septic shock in an otherwise healthy 30-year-old, and this fact helped guide our treatment decisions. We considered meningococcemia, gram-negative sepsis, group A streptococcal endotoxic shock, *Staph. aureus*, and — less likely, but a consideration because of the appearance of the rash — a rickettsial infection. Although we could not

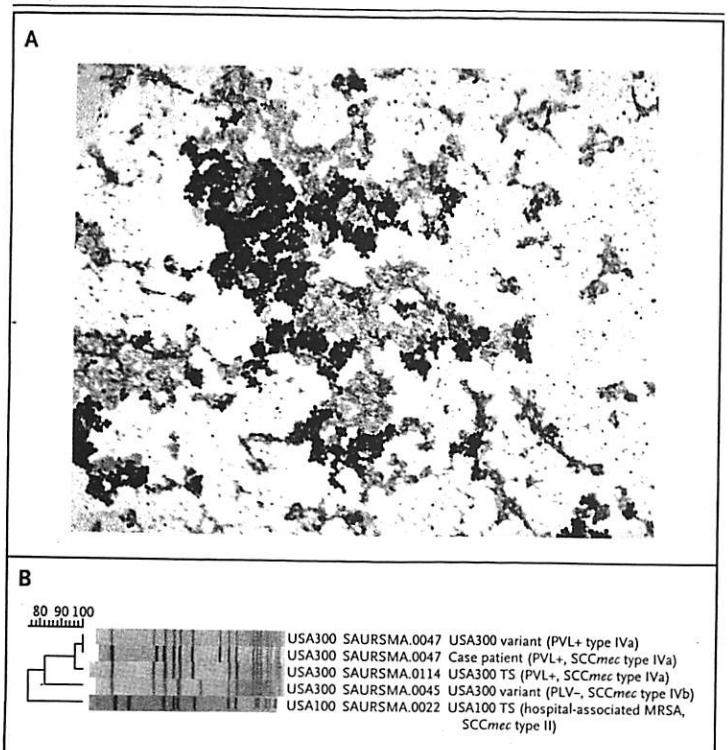

Figure 3. Bacteriologic Studies.

Gram's staining of the patient's blood culture shows gram-positive cocci (Panel A). A dendrogram of the results of pulsed-field gel electrophoresis (PFGE) typing (with the use of SmaI restriction endonuclease) of the patient's *Staphylococcus aureus* isolate, performed at the Centers for Disease Control and Prevention (CDC), shows identity with USA300 strain 0047 (Panel B). PVL denotes Panton–Valentine leukocidin; SAURSMA *Staphylococcus aureus*–resistant, digested with SmaI restriction enzyme; SCC staphylococcal cassette chromosome; and TS type strain. (PFGE analysis and dendrogram courtesy of Gregory Fosheim and Brandi Limbago, CDC.)

rule out any of these organisms initially and treated the patient for all of them, our leading diagnosis on the basis of her clinical presentation, her previous MRSA infection, and the pustular appearance of her rash was sepsis due to MRSA, with widespread metastatic staphylococcal disease.

CLINICAL DIAGNOSIS

Sepsis due to community-acquired methicillin-resistant *Staphylococcus aureus.*

DR. ROBERT C. MOELLERING, JR.'S DIAGNOSIS

Sepsis due to community-acquired methicillin-resistant *Staphylococcus aureus.*

PATHOLOGICAL DISCUSSION

Dr. Mary Jane Ferraro: After about 20 hours of incubation, two of four blood-culture bottles grew gram-positive cocci in clusters (Fig. 3A); the results were immediately reported to the health care providers. The blood culture isolate was identified as MRSA, with the same susceptibility profile as the isolate from the cultures of her leg wound 1 month earlier: resistance to oxacillin, erythromycin, and levofloxacin, but susceptibility to clindamycin (no inducible resistance), rifampin, tetracycline, trimethoprim–sulfamethoxazole, and vancomycin. Tests of the urine, a pustular lesion that was present on admission, and a nasal swab were also positive for MRSA. The strain, which was referred to the Centers for Disease Control and Prevention for testing and typing of toxins, was positive for PVL toxin and negative for the TSST-1 toxin, staphylococcal enterotoxins, and superantigens (A, B, C, D, E, and H). It was found to be strain USA300, subtype 0047 (Fig. 3B), which is the second-most-common pattern in the United States. The USA300 strain carries the SCC*mec* type IVa and almost always includes the PVL locus. The final diagnosis in this case was sepsis due to community-acquired MRSA, strain USA300-0047, PVL positive.

Dr. Harris: Are there questions for any of our speakers?

A Physician: This patient had musculoskeletal pain that seemed to be disproportionate to her injury several days before admission. In bloodstream infections, particularly meningococcal infections, there can be severe muscle pain — often in the lower back or anterior thigh — in the absence of other features of infection. Do you think that her severe pain (rated at 10 on a scale of 0 to 10, with no soft-tissue or other injuries observed) could have served as an early red flag for a serious bloodstream infection?

Dr. Moellering: It is possible. As you noted, muscle pain is often noted by patients with bacteremia. The traumatized muscle could have served as a locus minoris resistentiae for infection seeded by the bacteremia. I would wonder whether there was an early pyomyositis in that area.

Dr. Harris: Since this patient's death, I am aware of at least one other patient who has died at this hospital with a strikingly similar history and clinical presentation.

Dr. Nesli Basgoz (Infectious Diseases): These

cases illustrate the fact that although community-acquired MRSA typically results in localized skin lesions, systemic infection with sepsis may occur in patients who are known to harbor community-acquired MRSA, even after apparently successful treatment of the lesions. In particular, presentation with localized and then generalized musculoskeletal aches in a patient with a history of a skin infection caused by community-acquired MRSA should possibly prompt early consideration of systemic infection.

PATHOLOGICAL DIAGNOSIS

Sepsis due to community-acquired methicillin-resistant *Staphylococcus aureus*, strain USA300-0047, PVL-positive.

This case was presented at the Medical Grand Rounds. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Nesli Basgoz and Lloyd Axelrod for their assistance in organizing the conference.

REFERENCES

1. Lowy FD. *Staphylococcus aureus* infections. N Engl J Med 1998;339:520-32.
2. Groom AV, Wolsey DH, Naimi TS, et al. Community-acquired methicillin-resistant Staphylococcus aureus in a rural American Indian community. JAMA 2001;286:1201-5.
3. Moellering RC Jr. The growing menace of community-acquired methicillin-resistant Staphylococcus aureus. Ann Intern Med 2006;144:368-70.
4. Diep BA, Stone GG, Basuino L, et al. The arginine catabolic mobile element and staphylococcal chromosomal cassette mec linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant Staphylococcus aureus. J Infect Dis 2008;197:1523-30.
5. Gorwitz RJ. Understanding the success of methicillin-resistant Staphylococcus aureus strains causing epidemic disease in the community. J Infect Dis 2008;197:179-82.
6. Okuma K, Iwakawa K, Turnidge JD, et al. Dissemination of new methicillin-resistant Staphylococcus aureus clones in the community. J Clin Microbiol 2002;40:4289-94.
7. DeLeo FR, Diep BA, Otto M. Host defense and pathogenesis in Staphylococcus aureus infections. Infect Dis Clin North Am 2009;23:17-34.
8. Li M, Diep BA, Villaruz AE, et al. Evolution of virulence in epidemic community-associated methicillin-resistant Staphylococcus aureus. Proc Natl Acad Sci U S A 2009;106:5883-8.
9. Chambers HF. Pathogenesis of staphylococcal infection: a manner of expression. J Infect Dis 2009;199:291-3.
10. Loughman JA, Fritz SA, Storch GA, Hunstad DA. Virulence gene expression in human community-acquired Staphylococcus aureus infection. J Infect Dis 2009;199:294-301.
11. Stevens DL, Ma Y, Salmi DB, McIndoo E, Wallace RJ, Bryant AE. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant Staphylococcus aureus. J Infect Dis 2007;195:202-11.
12. Stevens DL, Wallace RJ, Hamilton SM, Bryant AE. Successful treatment of staphylococcal toxic shock syndrome with linezolid: a case report and in vitro evaluation of the production of toxic shock syndrome toxin type 1 in the presence of antibiotics. Clin Infect Dis 2006;42:729-30.